Chapter 3

Medical Nuclear, Biological, and Chemical (NBC) Defense Requirements and Research and Development Program Status

3.1 REQUIREMENTS

3.1.1 Introduction

Many countries and terrorist groups have acquired the means to produce chemical, biological and radiological weapons and the means to deliver them. Nuclear, biological, and chemical (NBC) proliferation increases the threat to deployed U.S. forces. In response, our medical chemical, biological, and radiological defense research programs' (MCBRDRP) mission is to preserve combat effectiveness by timely provision of medical countermeasures. Countermeasures are developed in accordance with joint service mission needs and requirements in response to chemical warfare (CW) threats, biological warfare (BW) threats, and threats associated with radiological/nuclear warfare (RW) devices. The MCBRDRP has three goals:

(1) Provide individual level protection and prevention to preserve fighting strength.
(2) Maintain technological capabilities to meet present requirements and counter future threats.
(3) Provide medical management of CW, BW, and RW casualties to enhance survivability, and expedite and maximize return to duty.

Chemical warfare agents are available worldwide and include vesicants (blister agents), nerve, blood, and respiratory agents. Biological threat agents include bacteria, viruses, rickettsiae, and toxins that can be produced by any group with access to a scientific laboratory or a pharmaceutical industrial facility. The primary nuclear threat is the use of conventional explosives to spread nuclear contamination over a limited area or strategic terrain (including usage against reactors or industrial radiation sources) and potentially the use of a single or a small number of crude, Hiroshima-type nuclear weapons. Exposure to multiple threats may result in synergistic effects. Assessment methodologies enable threat evaluation and injury prediction. Medical prophylaxis and treatment strategies reduce the performance decrement, injury, and death of military personnel in the field, thereby enabling them to accomplish their missions as well as reducing the need for medical resources.

DoD has maintained a medical research and development program for NBC for many years. This program has resulted in the fielding of numerous products to protect and treat service members. The DoD program to stockpile biological defense products has been smaller than the chemical defense effort, but has received greater emphasis in recent years.

Specific initiatives programmed to improve NBC defense medical readiness include:

- Continued emphasis on NBC medical countermeasures research.
- Identification and testing of medications and therapeutic regimens that reduce the effect of radiation on both bone marrow and the intestinal tract.
- A biological defense immunization policy for U.S. forces and for other-than-U.S. forces.
- Cooperative initiative with the U.S. Food and Drug Administration (FDA) for acceptance of efficacy data derived from animal studies as surrogates for large-scale human efficacy trials to license drugs and biological products that cannot be ethically tested for efficacy in humans.
- A prime systems contractor initiated effort to develop, license, produce, and store biological defense vaccines.
- Enhanced medical diagnostic capability for diseases/injuries caused by all agents.
- Definition of low-dose-radiation interaction on susceptibility to biological and chemical agents.

3.1.2 Challenges in the Medical NBC Warfare Defense Programs

Medical prophylaxes, pretreatments, and therapies are necessary to protect personnel from the toxic or lethal effects of exposure to all validated threat agents, as well as other anticipated threats. DoD has fielded a number of medical countermeasures that greatly improve individual medical protection, treatment, and diagnoses.

The DoD complies with the Food, Drug and Cosmetic Act for Drugs and Public Health Services Act Section 351 for biologics to ensure that drug products are safe and efficacious and biological products are safe, pure, and potent. DoD is working closely with the FDA to amend the Code of Federal Regulations (CFR) for New Drug and Biological Products that cannot meet the efficacy studies required by the FDA for product licensure because they are either not feasible and/or cannot ethically be conducted under the FDA's regulations for adequate and well controlled studies in humans. (See 21 CFR Sec 312.21(2)(b).) DoD presented a proposal to the FDA's Vaccines and Related Biological Products Advisory Committee to use animal efficacy data as evidence demonstrating the efficacy of the Pentavalent Botulinum Toxoid (ABCDE). The Advisory Committee recommended that the FDA accept DoD's proposed animal surrogate data for licensure of the Pentavalent Botulinum Toxoid (ABCDE). The FDA drafted a proposed rule that allows the use of animal efficacy data for those products that either cannot be tested ethically in humans or it is unfeasible to test. This proposed rule is expected to be published in the Federal Register in the near future.

Medical NBC defense products are thoroughly evaluated and tested for their safety in accordance with FDA guidelines before administration to *any* personnel. All NBC defense medical products must be safe to use and not degrade operational performance. In cases where adverse effects are known or are possible, a decision must be made—and a risk accepted—of the real or potential effects of a medical product versus the catastrophic effects of NBC weapons. In those cases where efficacy is not understood, the safety profiles of the products are well delineated. In many cases, the safety is well understood because the medical products have been widely

used to treat other medical conditions. (The anthrax vaccine is licensed and has been used since the 1970s to vaccinate veterinarians, textile workers, and others. The Pentavalent Botulinum Toxoid (ABCDE) was administered safely over 10,000 times to laboratory workers prior to its use for military personnel during the Gulf War. Various anti-emetics to protect against radiological threats have been used to treat cancer patients undergoing radiation therapy.) Several studies performed at the U.S. Army Medical Research Institute of Infectious Diseases demonstrated the efficacy of the anthrax vaccine against inhalation anthrax in the monkey model. Rhesus monkeys were vaccinated with one or two doses of the anthrax vaccine and then challenged with highly lethal levels of spores from the Ames strain of anthrax, the most virulent strain tested. In all these studies, the anthrax vaccine protected 42 of 43 monkeys against inhalation anthrax while none of a total of 14 controls used in these experiments survived.

The acquisition life cycle of medical products developed by DoD is normally managed in accordance with the guidelines found in DoD Regulation DoD 5000.2-R. However, since DoD also complies with FDA requirements, it also must follow the requirements of Title 21, Food & Drugs, Code of Federal Regulations for the manufacture, testing, and licensing of medical products. The following chart illustrates the correlation of FDA requirements for product development with the requirements of DoD 5000.2-R for the life cycle of product development in accordance with DoD acquisition policy:

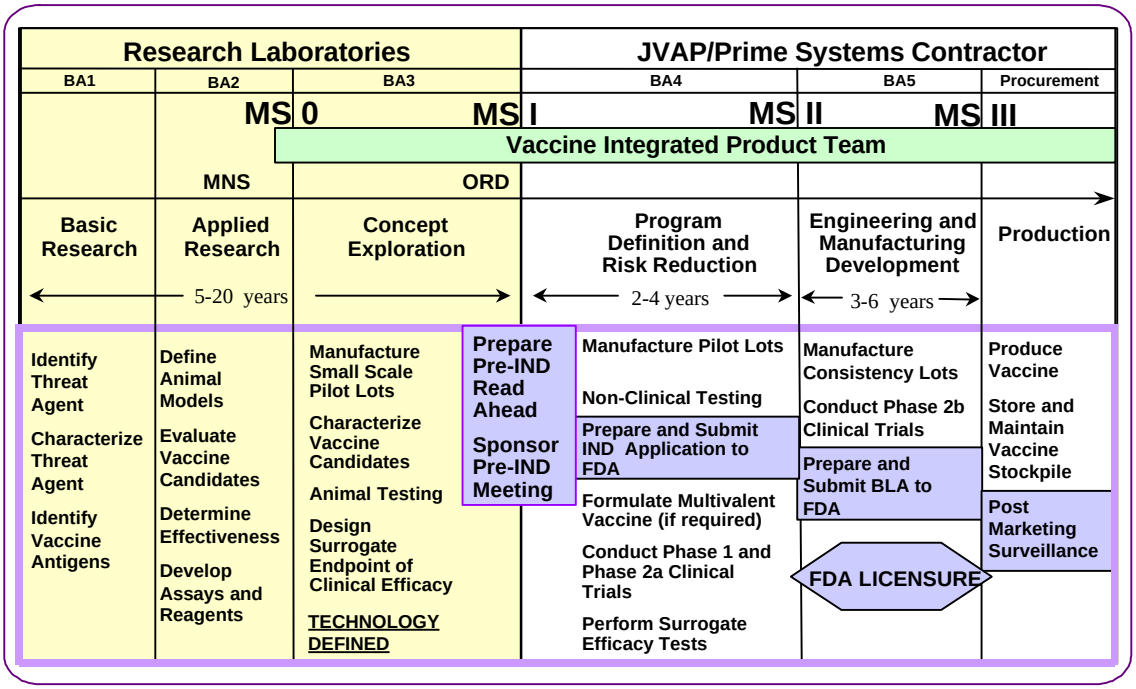

Figure 3-1. Integration of FDA and DoD Milestone Requirements

The medical NBC defense research programs discussed in this section are divided into chemical, biological, and nuclear areas of research. Table 3-3 (on page 3-15) provides a summary of the medical NBC defense programs and the planned modernization strategy over the next fifteen years.

3.1.3 Reducing Reliance on Research Animals

In accordance with the FY95 National Defense Authorization Act, which directed DoD to establish aggressive programs to reduce, refine, or replace the use of research animals, the MCBRDRP utilizes and develops technologies that will reduce reliance on animal research. In FY98, the MCBRDRP utilized computerized molecular modeling, computer predictions, *in vitro* cell cultures, a cell-free reaction system, and a lipid bilayer system to replace the use of animals when possible. All research proposals that use animals are evaluated by a statistician to ensure that the minimum number of animals required to obtain scientific validity are used. Animals lower on the phylogenetic scale (or the least sentient species) are used if the selection will permit attainment of the scientific objective. Additionally, all procedures that might cause pain or distress in laboratory animals are reviewed by a veterinarian with expertise in laboratory animal medicine to determine the procedural modifications, analgesics and/or anesthetic regimens to be incorporated to minimize pain or distress.

DoD policy states that animal use will be conducted in full compliance with the Animal Welfare Act and that animals are to be used in research only when scientifically acceptable alternatives are not available.

3.1.4 Medical Program Organization

Chemical/Biological. The U.S. Army is the Executive Agent for the Medical Chemical and Biological Defense Research Program as prescribed in DoD Directive 5160.5 and, as such, is the lead requirements coordinator. The programs are integrated DoD in-house and external efforts. The Joint Technology Coordinating Group (JTCG) 3 (Medical CW Agent Defense) and JTCG 4 (Medical BW Agent Defense) of the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee are responsible for the programs' joint consolidation, coordination, and integration. The ASBREM Committee maximizes efficiency by coordinated planning, and minimizes unnecessary program overlaps and costly materiel retrofits. (The integration of program management and oversight of medical and non-medical NBC defense programs is described in Chapter 1.) The Army Science and Technology Base Master Plan, the Defense Technology Area Plan, the Joint Nuclear Biological Chemical Defense Research, Development, and Acquisition Plan, and the Medical Science and Technology Master Plan are the program drivers for the chemical and biological research programs. The Joint Service Integration Group (JSIG) established a Medical Program Sub-Panel (MPSP), which is the user representative from the medical community, to establish and direct joint service NBC medical defense program requirements. The science and technology base is managed through the development and execution of Defense Technology Objectives (DTOs) and Science and Technology Objectives (STOs). The predevelopment program (basic research, exploratory development, and concept exploration and definition) is directed by the U.S. Army Medical Research and Materiel Command (USAMRMC) through its lead laboratories for medical chemical defense, biological defense, and infectious disease research, U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID), and Walter Reed Army Institute of Research (WRAIR), respectively. The

advanced development program (Program Definition and Risk Reduction [PDRR]) and Engineering and Manufacturing Development (EMD) for medical *chemical* defense products is directed by the U.S. Army Medical Materiel Development Activity (a USAMRMC asset). The advanced development program (PDRR and EMD) for medical *biological* defense products is directed by the Joint Program Office for Biological Defense (JPO-BD). The Joint Vaccine Acquisition Program (JVAP) acts as a subordinate element of JPO-BD to transition candidate biological defense vaccines from research laboratories to the Prime Systems Contractor for the development, testing, licensure, production, and storage of vaccine stockpiles.

Nuclear. The study of the medical and biological effects of ionizing nuclear radiation is performed by the tri-service Armed Forces Radiobiology Research Institute (AFRRI). AFRRI programs are integrated into other DoD in-house and external efforts under the coordination of ASBREM. Specific requirements and tasking for AFRRI research comes from the individual services, Joint Staff, and the Defense Technology Objectives (DTOs) through the authority of a Board of Governors (BOG) with funding from the Director, Defense Research and Engineering (DDR&E) under the Secretary of Defense for Acquisitions and Technology. AFRRI is under the administrative control of the Uniformed Services University of the Health Sciences (USUHS). Members of the AFRRI BOG include representatives of Under Secretary of Defense for Acquisition and Technology (USD(A&T)), the Assistant Secretary of Defense for Health Affairs (ASD(HA)), the Surgeons General of the Army, Navy, and Air Force, and the Deputy Chiefs of Staff for Operations of the Army, Navy, and Air Force, or their designated representatives. Major inputs to AFRRI research requirements are driven by the biennial Army Qualitative Research Requirements (QRR) compiled by the U.S. Army Nuclear and Chemical Agency (USANCA) and AFFRI's four DTOs. Currently there is no established advanced development (PDRR and EMD) process for the nuclear medical program.

3.2 MEDICAL CHEMICAL DEFENSE RESEARCH PROGRAM

The mission of the Medical Chemical Defense Research Program (MCDRP) is to preserve combat effectiveness by timely provision of medical countermeasures in response to joint service chemical warfare defense requirements.

3.2.1 Goals

The goals of the MCDRP are the following:

- Maintain technological capability to meet present requirements and counter future threats:

  - Determine sites, mechanisms of action, and effects of exposure to chemical warfare agents with emphasis on exploitation of neuroscience technology and dermal pathophysiology.
  - Identify sites and biochemical mechanisms of action of medical countermeasures.
  - Exploit molecular biology and biotechnology to develop new approaches for medical countermeasures.
  - Exploit molecular modeling and quantitative structure-activity relationships

supporting drug discovery and design.

- Provide individual-level prevention and protection to preserve fighting strength:

  - Develop improved prophylaxes, pretreatments, antidotes, and therapeutic countermeasures.
  - Develop skin protectants and decontaminants.
  - Identify factors that influence safety and efficacy properties of candidate countermeasures.
  - Develop and maintain preformulation, formulation, and radiolabeling capabilities.

- Provide medical management of chemical casualties to enhance survival and expedite and maximize return to duty:

  - Develop concepts and recommend therapeutic regimens and procedures for the management of chemical casualties.
  - Develop diagnostic and prognostic indicators for chemical casualties.
  - Provide education on medical management of chemical casualties.

3.2.2 Objectives

The objectives of the MCDRP differ with the varying threats:

- For vesicant (or blister) agents, the objective is to develop a pathophysiological database on vesicant chemical agents and a working hypothesis on how damage occurs at the cellular level. Used with associated technologies, this approach will enable the formulation of definitive pretreatment and treatment strategies, and is expected to produce a realistic concept for medical prophylaxis, immediate post exposure therapy, and topical protection. Alternatively, in dealing with liquid agent threat, reactive topical skin protectants (rTSPs) can be developed that will protect the skin and simultaneously detoxify the agent.

- For nerve agents, the objective is to field a safe and effective advanced anticonvulsant nerve agent antidote, and to field an advanced pretreatment based on biological scavengers like human enzyme butyrylcholinesterase (BuChE). Like acetylcholinesterase, the target enzyme for nerve agents, native BuChE is also inhibited by nerve agents. Through bioengineering efforts in the technology base, human BuChE has been mutated to a form that catalyzes the breakdown of nerve agent. The concept of using a catalytic BuChE to protect against large doses of nerve agent has been established in laboratory animals, indicating that this approach is feasible in humans. Although both offer potential long term protection, the enzyme pretreatment requires a single dose rather than three doses daily of pyridostigmine bromide.
- For blood agents, the objective is to develop and field a safe and effective cyanide pretreatment.
- For respiratory agents, the objective is to develop prophylaxes and therapies by understanding pathophysiological changes after agent exposure.

3.2.3 Threats, Countermeasures, Technical Barriers, and Accomplishments

The chemical warfare threats and countermeasures, as well as chemical defense research and development technical barriers and accomplishments, are outlined in Annex D (Section D.1).

3.3 MEDICAL BIOLOGICAL DEFENSE RESEARCH PROGRAM

The mission of the Medical Biological Defense Research Program (MBDRP) is to develop medical countermeasures to protect U.S. forces and thereby deter, constrain, and defeat the use of biological agents against them (DoD Directive 5160.5, May 1985). The program is directed against agents of biological origin that are validated military threats. A primary concern is the development of vaccines, drug therapies, and diagnostic tools, and other medical products that are effective against agents of biological origin (see Table 3-1).

3.3.1 Goals

Goals of the MBDRP include the following:

- Protecting U.S. forces' warfighting capability during a biological attack.
- Reducing vulnerability to validated and novel threats by maintaining a strong technology base.
- Providing education on medical management of BW casualties.

3.3.2 Objectives

In accomplishing the goals of the MBDRP, efforts are focused on three objectives:

- Maintaining technological capability to meet present requirements and counter future threats:
  - Determine sites, mechanisms of action, and effects of exposure to biological warfare agents with emphasis on exploitation of molecular science.
  - Identify sites and biochemical mechanisms of action of medical countermeasures.
  - Exploit molecular biology and biotechnology to develop new approaches for medical countermeasures.
  - Exploit molecular modeling and quantitative structure-activity relationships supporting drug discovery and design.

- Providing individual-level prevention and protection to preserve fighting strength:
  - Develop improved vaccines, pretreatments, antidotes, and therapeutic countermeasures.
  - Identify factors that influence safety and efficacy properties of candidate countermeasures.

- Providing training in medical management of biological casualties to enhance survival and

expedite and maximize return to duty:

- Develop concepts and recommend therapeutic regimens and procedures for the management of biological casualties.
- Provide education on medical management of biological warfare casualties

The MBDRP responds to requirements from the DoD as identified in the Joint Service Agreement on Biological Defense, the Joint Warfighting Science and Technology (S&T) Plan, the Defense Technology Area Plan, the Defense S&T Strategy, and DoD Directive 6205.3, "Biological Defense Immunization Program".

Highly sophisticated technology base efforts for medical biological defense hold the promise of yielding important new products to protect our troops against a wide range of biological weapons and naturally occurring diseases. These products include multi-agent vaccines that will reduce costs of vaccine production and simplify immunization schedules, and a common diagnostic kit, a hand-held device that can be deployed at forward sites to rapidly analyze clinical samples for the presence of biological warfare agents as well as infectious diseases of military importance. The development of these products, as well as the complementary technology-based research and development to enhance and expand these capabilities and to identify and develop new capabilities, is also being supported by collaboration with other agencies, such as the Defense Advanced Research Projects Agency (DARPA) and the Department of Energy (DOE).

Projects and technologies shared with the DOE are related to the strengths of DOE laboratories in developing advanced technologies in order to enable rapid detection of and response to a chemical or biological incident. While DOE focuses internal technology development efforts on the domestic threat, they actively support the DoD. The work spans DNA sequencing and biodetection to modeling and simulation, collaborating on projects such as x-ray crystallography and nuclear magnetic resonance imaging of BW agent antigens. The DNA sequencing efforts have led to advances in developing "lab on a chip" diagnostic technology for several BW threat agents. DOE is not involved in protection and treatment of personnel, but they are assisting DoD with drug/chemical database searches with the intent of identifying novel inhibitors of pathogens.

The DARPA BW defense program includes collaborating with USAMRMC on new platforms to enhance delivery and effectiveness of multi-agent vaccines (for example, stem cells genetically programmed to express antigens sequentially in order to provide automatic boosters in the body). Multi-agent vaccines are similar to the measles-mumps-rubella vaccine administered to children except that the technologies being explored for producing these new vaccines are more advanced, relying on bioengineering technologies such as naked DNA and the replicon-based delivery systems. Research in both the naked DNA and replicon approaches is advancing rapidly, and transition of a multiagent vaccine to advanced development (post Milestone I) is scheduled for FY 02.

Bioengineering techniques are also being used to prepare a variety of recombinant vaccines against single threat agents that will be produced without the need to grow the actual threat agent during the vaccine production process. Several recombinant vaccines are scheduled to be fielded over the next 10 years.

Development of a common diagnostic kit is proceeding with two state-of-the-art technologies. In the antibody-based system, a membrane platform will detect biological warfare threat agents in biological specimens. The second system relies on detecting the DNA of a variety of biological warfare threat agents or natural infectious diseases by a hand-held polymerase chain reaction (PCR) technique. With these tools, clinical diagnoses will be made much faster (less than 30 minutes) and farther forward than is possible now. The development of technologies for common diagnostic systems is jointly supported by DARPA.

The MBDRP includes the following areas of research:

Pre-exposure Countermeasures: This area involves prophylactic measures undertaken to prevent illness and injury associated with exposure to bacterial, viral, and toxin threat agents. The primary focus of pre-exposure therapy is efforts to produce effective vaccines. The roles of various factors in stimulating cellular and humoral immunity are determined through study of specific genes or properties of threat agents. This knowledge provides tools for development of second-generation recombinant or multi-agent vaccine candidates as well as pretreatment therapies to intervene in the pathogenic effects of threat agents.

Post-exposure Countermeasures: Research efforts in this area are focused on developing safe, effective treatments to alleviate disease or injury associated with exposure to bacterial, viral, or toxin threat agents. Therapeutic measures may involve administration of antimicrobials, anti-toxins or generic compounds formulated to intervene at the pathogen's site of action. The know-ledge necessary to develop such products requires in-depth research in the basic pathogenesis and physiology of the BW agents. These analyses will afford researchers tools to create a universal approach in treating post-exposure casualties of a BW attack.

Diagnostics: Diagnostics research involves the investigation and evaluation of sensitive and specific methods for detection of infectious organisms, toxins, antigens and antibodies in biological materials to include the application of nucleic acid probes or synthetic antigens. Rapid identification tests and diagnostic methods for the assay of toxins, metabolites, and analogs in clinical specimens are major goals of this program area.

3.3.3 Threats, Countermeasures, Technical Barriers, and Accomplishments

A biological threat agent is defined as an intentionally disseminated living microorganism or toxin that can cause disease or death in humans, animals, or plants. Threat agents include a broad range of microorganisms (bacteria, rickettsiae, and viruses) and toxins of biological origin. Biological weapons are easy to make, difficult to detect, and can be very effective. Defense against this class of weapon is difficult, particularly when biological agents can produce casualties over an area of thousands of square kilometers. Biological agents could also be used with devastating effect in combination with nuclear, chemical, or conventional weapons.

Countermeasures and diagnostic techniques for biological weapons are shown in Table 3-1. Critical elements of medical biological defense include the ability to protect U.S. forces from

BW agents, to rapidly diagnose (in clinical specimens) infection or intoxication from agents, and to treat casualties. Currently, the most effective countermeasure is pre-deployment active immunization. Future threats, however, may involve genetically engineered biological weapons that may be easily produced, highly lethal, difficult to detect, and resistant to conventional therapies.

The current MBDRP includes the following research areas for the development of medical countermeasures:

- Characterize the biochemistry, molecular biology, physiology, and morphology of BW threat agents.
- Investigate the pathogenesis and immunology of the disease.
- Determine the mechanism of action of the threat agent in an animal model system.
- Select antigen(s) for candidate vaccines.
- Develop and compare potential vaccine candidates and characterize their effects in animal models.
- Establish safety and efficacy data for candidate vaccines.
- Develop medical diagnostics to include far forward, confirmatory, and reference lab.
- Develop chemo/immunotherapeutic agents and preparations.

Technical shortcomings in the private sector include the lack of high-level biological containment (BL-3 and BL-4) laboratory facilities to support biological defense research and scientific expertise in biological defense. These factors restrict the depth of expertise, facilities, and support available. A recent redress of funds and authorizations over a six year period (FY99-05) will be used for DoD facility upgrades and to maintain scientific and technological expertise.

Details of the biological warfare threats and countermeasures, as well as biological defense research and development technical barriers and accomplishments, are presented in Annex D (Section D.2).

Table 3-1. Medical Biological Defense Countermeasures and Diagnostic Techniques

VACCINES

- *Killed* – killed or inactivated microorganism that is incapable of replicating but stimulates immunity.
- *Live, attenuated* – live organism, genetically selected not to cause disease but able to stimulate immunity.
- *Toxoid* – toxin protein treated to inactivate its toxicity but retains its ability to stimulate immunity.
- *Recombinant* – gene coding for a protein that stimulates specific immunity to a BW agent is inserted into biological vector for production. Protein may be produced in high yields through bioengineering.
- *Deoxyribonucleic Acid (DNA)* – section of DNA that codes for protein that stimulates specific immunity to a BW agent. DNA produces the desired protein in recipient which stimulates immunity.
- *Polyvalent* – mixture of antigens that protects against a number of different BW agents.
- *Vectored* – carrier organism bioengineered to confer immunity against an unrelated BW agent or multiple agents.

ANTIBODY (ANTISERUM, ANTITOXIN)

- *Heterologous* – antibodies collected from animals (*i.e.*, different species than the recipient) repeatedly immunized against the BW threat. These antibodies must be treated to reduce the human immune response to them (serum sickness).
- *Homologous* – antibodies of human origin (*i.e.*, same species as the recipient) that provide protective immunity against the BW threat. These antibodies are not prone to stimulating serum sickness.
- *Monoclonal* – a cell culture technique for producing highly specific antibodies against a disease agent.
- *Bioengineered* – antigen binding site on the variable portion of an antibody elicited in a nonhuman system is combined with the nonvariable portion of a human antibody to produce a "humanized" antibody.

DRUGS

- *Antibiotics* – very effective against bacteria, but are ineffective against viruses and toxins.
- *Antiviral compounds* – Promising drugs in development by the pharmaceutical industry are being evaluated against biological threat viruses
- *Others* – compounds that offer new possibilities for protecting against and treating exposure to BW agents (such as drugs to treat toxins or nonspecifc treatments such as immunomodulators.)

DIAGNOSTIC TECHNOLOGIES

- *Immunological technologies* – These tests rely on antibodies for detecting the presence of proteins associated with the BW agent. They are easy to use, compact, rapid (minutes), and require little logistic support. This technology is currently used in out-patient clinics and doctor's offices.
- *Nucleic acid technologies* – nucleic acid tests, specifically the polymerase chain reaction (PCR), rely on segments of genes unique to BW agents to detect the presence of those agents. These tests are extremely sensitive and specific, but currently require more support to perform.

3.3.4 Defense Advanced Research Projects Agency (DARPA) Programs

As one of the major program areas conducted under its Defense Sciences Office, DARPA is pursuing the demonstration and development of new biological warfare defense capabilities. Major thrusts include real-time (environmental) sensing (described in Chapter 2); medical countermeasures (developing barriers to prevent entry of pathogens into the human body and developing pathogen countermeasures to block pathogen virulence and to modulate host immune response); Advanced Medical Diagnostics for the most virulent pathogens and their molecular mechanisms; and Consequence Management Tools.

Medical countermeasures to be developed include: (1) multi-agent therapeutics against known, specific agents, and (2) therapeutics against virulence pathways (mechanisms of disease) shared by broad classes of pathogens. Specific approaches include modified red blood cells to sequester and destroy pathogens, modified stem cells to detect pathogens and to induce immunity or produce appropriate therapeutics within the body, identification of virulence mechanisms shared by pathogens, development of novel therapeutics targeting these mechanisms, and efficacy testing in cell cultures and animals.

Early diagnosis is key to providing effective therapy against BW agents since many of these agents cause early nonspecific flu-like symptoms. The goal of the DARPA Advanced Medical Diagnostics thrust is to develop the capability to detect the presence of infection by biological threat agents, differentiate from other significant pathogens, and identify the pathogen, even in the absence of recognizable signs and symptoms (when the pathogen numbers are low).

Mission effectiveness requires rapid, correct medical responses to biological threats. The objective of the Consequence Management thrust is to provide comprehensive protocols to protect or treat combatants by using current and emerging biological countermeasures. It will provide accelerated situational awareness for biological agents events by detecting exposure to agents through an analysis of casualty electronic theater medical records, and will locate and determine the most effective logistical support for providing appropriate treatment and pathogen-specific resources required to mitigate effects of the attack.

3.4 MEDICAL NUCLEAR (RADIOLOGICAL) DEFENSE RESEARCH PROGRAM

The mission of the Medical Nuclear Defense Research Program (MNDRP) is to conduct research in the field of radiobiology and related matters essential to the support of DoD and the Military Services. The sole repository of defense radiobiology expertise is AFRRI.

3.4.1 Goals

The goals of the MNDRP are the following:

- Develop medical countermeasures for the acute, delayed, and chronic effects of radiation.
- Identify and quantify hazards of embedded depleted uranium shrapnel to military casualties, both female and male.
- Develop rapid bioassay for radiation injury suitable for field deployment.
- Produce improved chelating agents for use in treating internal contamination by radioactive heavy metals.
- Sustain combat capability, increase survival, and minimize short- and long-term health problems associated with ionizing radiation alone, and when radiation is combined with other weapons of mass destruction.
- Respond to immediate operational requirements that require expertise in either radiation medicine, health physics, or radiobiology.
- Maintain core of scientific expertise necessary to meet current research requirements and to counter current and future radiological threats.

- Provide nuclear radiation weapon effects medical training for DoD medical personnel.

3.4.2 Objectives

The primary objective of this research group is to address the major aspects of military operational requirements for dealing with radiation injuries. A nuclear threat agent is any weapon that causes detrimental medical effects by either direct external irradiation or by internal contamination with radioactive material. These agents include radiation dispersal weapons, which scatter radioactive material with conventional explosives; deliberate area contamination; destruction of a nuclear power plant; improvised nuclear devices; and traditional nuclear weapons. Operational requirements include programs in casualty management, medical radioprotectants to diminish radiation injury, medical therapeutic regimens, maintenance of performance, and radiation hazards assessment.

3.4.3 Threats, Countermeasures, Technical Barriers, and Accomplishments

The deployment of a relatively low-yield nuclear device is increasingly possible by a terrorist or third-world country. If counterproliferation and intelligence efforts fail to deter deployment, medical remediation of casualties must be available. Such a device would most likely be utilized against either a military installation or a political target (*e.g.*, the seat of government, large population center, or commercial port city). In such a scenario, citizens outside the immediate lethal area would be exposed to the prompt radiation of the initial explosion as well as to chronic exposures resulting from the residual radioactive fallout.

The nuclear weapons inventory of current adversaries is thought to be small, but if a weapon is used for military advantage, concomitant use of biological or chemical weapons should be anticipated. A radiation dispersal device could include the destruction of a nuclear reactor, contamination of a battlefield with nuclear waste, or deliberate radioisotope contamination of a terrorist car bomb-type conventional explosives attack. Most casualties in these scenarios would suffer non-lethal doses of external irradiation. This would complicate the management of their conventional injuries and could cause internal contamination with radionuclides. Early radiation injury diminishes the soldier's ability to fight and survive. Effective radiation countermeasures must protect the soldier from performance decrement and simultaneously diminish lethality and the long-term effects of radiation injury. Therapeutic measures will increase the survival and diminish the morbidity of individual soldiers who are wounded by radiation. A research program to understand molecular and cellular damage induced by radiation is needed to determine the best medical countermeasures for the new radiogenic wounding agents on the modern battlefield. Table 3-2 presents an overview of countermeasures to radiological exposure and research accomplishments during FY 98.

Table 3-2. Medical Nuclear Defense Countermeasures

PRETREATMENTS

Multidrug combinations: Enhanced survivability has been shown in animal models using a combined aminothiol and cytokine treatment modality. Sustained and effective delivery of prophylactic drugs was demonstrated in animal models using implanted capsules.

Antiemetics: Granisitron (Kytril®) has been adopted as the NATO standard pretreatment antiemetic medication to significantly block performance-degrading early symptoms of radiation injury. This allows mission completion and consequently diminishes the overall casualty rate.

DEPLETED URANIUM TOXICITY

Metabolism of metallic uranium fragments: Prior to the wounding of soldiers in Desert Storm, very little was known about the toxicity of implanted metallic uranium fragments. Previous uranium toxicity studies had been limited to inhaled uranium oxides in uranium workers. Preliminary aspects of animal studies indicate distribution to depot sites throughout the body and potential risks of late effects. Adequate chelation therapy does not exist at this time to increase excretion of this material.

Fetal metabolism of depleted uranium: During the next conflict it is anticipated that young female soldiers will be wounded by enemy depleted uranium weapons. No knowledge exists of the effects of this material on subsequent pregnancies.

MEDICAL THERAPIES

Specific Cell Line Stimulants: Granulocyte-Macrophage Colony Stimulating Factor has been demonstrated to be highly effective in restoring the immune competence of the bone marrow and allowing survival from radiation injuries previously considered lethal. The cytokine thrombopoietin has been developed as a therapeutic agent and is undergoing further trials as a platelet-formation stimulant.

Broad Range Cellular Recovery Stimulants: Research continues into biologically stable compounds that stimulate recovery of multiple hematopoietic cell lines.

Susceptibility to Infectious Agents and Efficacious Therapy: Research continues to assess susceptibility and resistance to infectious agents in conjunction with use of prompt and chronic sublethal irradiation, and to develop combined modality therapies that attack microorganisms and enhance innate immune response in irradiated personnel. A significant reduction in mortality was shown in animal models using a clinical support protocol based on antibiotic and platelet transfusion regimens.

DIAGNOSTIC TECHNIQUES

Biodosimetry and Dose Assessment: No dose-assessment method other than individual physical dosimeters can be made available currently to deployed soldiers. Automated chromosome dicentromeric analysis has been developed and can be made deployable to the Echelon 3 medical care level, and other, more rapid, methods are being evaluated.

CHEMICAL AND BIOLOGICAL WARFARE INTERACTIONS WITH RADIATION

Increased lethality of biological weapons after low level irradiation: Ongoing studies indicate even low levels of radiation exposure will markedly increase the infectivity of biological weapons. Existing data suggest synergistic interactions of mustard and nerve agents with ionizing radiation.

Significant progress has been made in prophylactic and therapeutic measures that will reduce mortality and morbidity in high-dose radiation environments. During the Cold War, the number of casualties resulting from the large-scale deployment of nuclear weapons would have easily overwhelmed the medical assets of NATO forces. In the current threat environment, adequate planning for medical response to a very limited nuclear attack is mandatory. While casualty numbers from a nuclear detonation will still be large, countermeasures have been developed that will significantly limit the morbidity and the secondary mortality. These modalities

will be particularly important in the likely scenario of terrorist use of radiation weapons. If the attack is limited to one or, at worst, a small number of events, the ability to provide intensive, sophisticated medical and other support is highly credible because of the availability of uncompromised treatment/research centers and medical evacuation capabilities.

Details of the radiological threats and countermeasures, as well as nuclear defense research and development technical barriers and accomplishments, are presented in Annex D (Section D.3).

3.5 MEDICAL NBC RESEARCH PROJECTION

Table 3-3 presents a projection of the medical NBC defense programs and modernization strategy for the next 15 years.

Table 3-3. Medical NBC Defense Programs and Modernization Strategy

	NEAR (FY99-00)	MID (FY01-05)	FAR (FY06-15)
Medical Chemical Defense	**Licensed topical skin protectant**	**Licensed advanced anticonvulsant** **Licensed cyanide pretreatment** **Licensed multichambered autoinjector**	**Licensed reactive topical skin protectant** **Licensed advanced prophylaxis for chemical warfare agents** **Licensed specific protection and treatment for blister agents (vesicant agent countermeasures)** **Licensed vesicant agent prophylaxis**
Medical Biological Defense	**Anthrax vaccine Amendment for new dosing schedule** **Licensure of Pentavalent Botulinum Toxoid (ABCDE) Adsorbed**	**Licensed Q fever vaccine** **Licensed tularemia vaccine** **Licensed Vaccinia, cell culture derived vaccine** **Licensed Botulinum A/B/E/F monovalent vaccines** **Licensed new Venezuelan Equine Encephalomyelitis (VEE) vaccine** **Licensed brucellosis vaccine**	**Licensed staphylococcal enterotoxin B (SEB) vaccine** **Licensed new plague vaccine** **Licensed combined VEE, Western Equine Encephalomyelitis (WEE), & Eastern Equine Encephalomyelitis (EEE) vaccine** **Multiagent vaccine delivery system** **Hand-Held Common Diagnostic System** **Licensed Botulinum Tetravalent vaccine** **Licensed Ricin vaccine**
Medical Nuclear Defense	**Depleted uranium fragments toxicity assessment** **Multidrug radioprotectants validated** **Combination cytokine therapy validated** **Risk assessment for low dose, low dose-rate radiation effect**	**Radioprotectant transdermal patches** **New-generation prophylactic and therapeutic immunomodulators for multiorgan injuries** **Computer models to understand effects resulting from combined NBC attacks** **Echelon 3 biodosimetry system** **Carcinogenicity assessment of DU**	**Licensed radiation-induced cancer/mutation preventive techniques** **Licensed countermeasure for chem-bio-radiation interaction** **Echelon 2 biodosimetry system**

3.6 MEDICAL R&D REQUIREMENTS ASSESSMENT

ISSUE: **DoD does not have a current approved mechanism for licensure of chemical and biological defense medical products (*i.e.*, drugs and vaccines) because legal and ethical constraints prevent adequate full testing in humans.**

SOLUTION*:* The FDA and DoD are working together to amend the Code of Federal Regulations to allow animal efficacy data to be used in lieu of large-scale human clinical efficacy trials. This mechanism of licensure is vital to provide military service personnel with licensed products. This rule will also establish requirements for licensure and allow the DoD to plan and conduct the appropriate studies to obtain product approval for the products planned for production and licensing. A proposal for the licensure of Botulinum Pentavalent Toxoid using the guinea pig as a surrogate model in lieu of human testing was accepted by a FDA Advisory Committee. The DoD is completing the clinical testing of Botulinum Pentavalent Toxoid for submission of this data to the FDA with projected licensure of this product in FY00.

ISSUE: **DoD lacks FDA-licensed vaccines against BW threat agents.**

SOLUTION: DoD awarded a prime systems contract to DynPort LLC. This contract establishes a single integrator to develop, license, produce, and maintain a stockpile of BD vaccines for protection against BW agents. DynPort LLC is required to obtain and maintain FDA licensure for all the vaccine products developed and produced under this contract by conducting clinical trials and establishing manufacturing procedures.

The contract was awarded in November 1997 and begins with the development and licensure of three vaccines: Q fever, Tularemia, and Vaccinia, and the storage of the current unlicensed BD vaccine stockpile (IND products). There are options for the development and licensure of ten other BD vaccines, which are programmed for development and licensure by FY10.

ISSUE: **Anthrax vaccine issues. Anthrax vaccination currently requires a primary series, six dose regimen spaced out over the course of 18 months, with an annual booster to maintain immunity. The timetable for the vaccination series makes it difficult to complete before deployment of forces or to ensure that mobile forces, once deployed, are administered the proper regimen.**

SOLUTION: On 18 May 1998, DoD decided to systematically vaccinate all U.S. military personnel against anthrax. Current plans call for personnel serving in high threat regions to receive vaccinations, which began in summer 1998. The manufacturing process for the anthrax vaccine has met all FDA requirements for producing and shipping the vaccine safely and contaminant-free. As of February 1999, more than 184,000 military personnel have received shots of the anthrax vaccine. Total force vaccination will follow according to a schedule. This decision is crucial for developing a strategy to maintain the industrial base capability for vaccine production.

A firm fixed price contract to purchase Anthrax Vaccine Adsorbed for the continued supply of anthrax vaccine was awarded negotiated and signed for a 2 year period. DoD continues to work with BioPort to meet the more stringent requirements the FDA has imposed on all vaccine manufacturer. DoD has provided technical guidance on testing and evaluation and the auditing of quality systems. DoD conducted preliminary testing of a reduction of the dosage regime for Anthrax Vaccine Adsorbed from six vaccinations to five over an 18 month period. The results of this study will be presented to the FDA in FY 99. For more information on the DoD anthrax vaccine program, visit "Concerning the Anthrax Threat" on the Internet at http://www.defenselink.mil/specials/Anthrax.

ISSUE: **The effects on humans resulting from the exposure to low doses of chemical agents, particularly organophosphate (nerve) agents, are not clearly understood.**

***SOLUTION*:** Beginning in FY96, DoD, in association with the Research Working Group of the Interagency Persian Gulf Veterans' Coordinating Board, DoD dedicated $5 million to evaluate the chronic effects of low-dose level exposure to chemical agents. Studies are underway since 1QFY97 to develop highly specific and sensitive assays, preferably forward-deployable, to detect and potentially quantify low-level exposure to chemical agents. These ongoing studies may also identify any long-lasting and toxic metabolites of chemical agents that could account for delayed and long-term health consequences. In addition, studies to look at the impact of possible genetic polymorphisms of cholinesterase enzymes upon individual response to nerve agents are underway. Additional funds have been committed and contracts are being awarded to evaluate potential chronic health complaints resulting from exposure to nerve agents. These contracts were begun 1QFY98.

ISSUE: **Radiation exposures below a level that cause acute effects predispose military personnel to injury from other battlefield agents. The magnitude of this interaction has not been fully evaluated.**

SOLUTION: Definitive assessment of NBC threat interactions and NBC agent modeling will support the strategic design and development of specific preventive and treatment countermeasures.

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